

Remarks/Arguments

Claims 1-3, 5-7, and 13-15 were originally pending. Claims 4, 8, 9-12 and 16-70 were previously canceled. Claims 1-3, 5, 7, and 13-15 are now pending. Claims 1-3, 5, 7, and 13-15 have been rejected. Applicants ask that all pending claims be reexamined in view of the following arguments.

Rejection Under 35 U.S.C. §103(a)

The Examiner has rejected claims 1-3, 5-7, and 13-15 under 35 U.S.C. 103(a) as being unpatentable over Fabian *et al.* (J. Cell Biochem., 1993, 17G: 153-160, IDS) in view of Sauter *et al.* (British J. Cancer, 1997, 76(4): 494-501, IDS), JAMA (JAMA, 1973, 224 (6): 823-827), and Knight *et al.* (Ann. Clin. Res., 1980, 12(15): 202-207).

The Examiner argues that Fabian *et al.* teaches a method of providing and cytologically examining ductal fluid obtained via fine needle aspiration from high and low risk women. The Examiner further states that Fabian *et al.* does not teach obtaining ductal epithelial cells by nipple aspiration of the milk ducts or by ductal lavage of at least one breast milk duct nor does it teach providing the ductal fluid sample comprises receiving a sample which had been previously obtained. The Examiner then argues that these deficiencies are made up for in the teachings of Sauter, JAMA and Knight *et al.*

The Examiner argues that Sauter *et al.* teaches a non-invasive method for the early detection of breast cancer comprising collecting nipple aspirate fluid from a patient, cytologically analyzing the fluid (e.g. computerized image analysis of nipple aspirate fluid epithelial cells), and evaluating the promising cancer markers, wherein the patients were categorized by their risk for breast cancer as having no risk factors, a first degree relative with breast cancer, a history of curative treatment for

ductal carcinoma in situ (DCIS), or invasive breast cancer, precancerous mastopathy, atypical hyperplasia (AH) or lobular carcinoma in situ (LCIS) or recently diagnosed invasive cancer or the breast.

The Examiner then argues that the JAMA reference teaches a method for early detection of breast cancer in a patient comprising a) removing fluid through nipples with a suction device or by a method comprising hair-like catheters into breast ducts with the help of an operating microscope, flushing the ducts with saline for cell studies and b) examining the fluid to identify abnormal cells. The Examiner then states that the JAMA reference discloses using said method to study breast fluid from patients without signs of breast disease.

Lastly, the Examiner argues that Knight *et al.* teaches that estrogen receptor (ER) has now replaced clinical criteria in the selection of patients for endocrine therapy and that patients whose tumors do not contain ER should not be subject to hormonal manipulation.

The Examiner argues that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Fabian et al. to obtain ductal epithelial cells by nipple aspiration or ductal lavage of at least one breast milk duct as taught by Sauter or JAMA reference instead of fine needle aspiration. The Applicants respectfully disagree.

Applicants respectfully traverse the foregoing rejection on the grounds that the Examiner has failed to establish a *prima facie* case of obviousness, since Fabian, *et al.*, Sauter, JAMA, or Knight *et al.*, alone or in combination, fail to teach or suggest the claimed invention and further fail to provide the necessary motivation or expectation of success for the ordinarily skilled artisan to arrive at the claimed invention.

To establish a *prima facie* case of obviousness, it is necessary for the Examiner to present evidence, preferably in the form of some teaching, suggestion, incentive or inference in the applied

references, or in the form of generally available knowledge, that one having ordinary skill in the art would have been motivated to make the claimed invention and would have had a reasonable expectation of success in making the claimed invention. Under section 103, "[b]oth the suggestion and the expectation of success must be founded in the prior art, not in applicant's disclosure" (*Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.* 927 F.2d 1200, 1207, 18 USPQ2d 1016 (Fed. Cir. 1991), quoting *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed Cir. 1988)).

Moreover, when a combination of references are used to establish a *prima facie* case of obviousness, the Examiner must present evidence that one having ordinary skill in the art would have been motivated to combine the teachings in the applied references in the proposed manner to arrive at the claimed invention. See, e.g., *Carella v. Starlight Archery*, 804 F.2d 135, 231 USPQ 644 (Fed. Cir. 1986); and *Ashland Oil, Inc. v. Delta Resins and Refractories, Inc.*, 776 F.2d 281, 227 USPQ 657 (Fed. Cir. 1985).

"[C]ase law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references. ... Combining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability--the essence of hindsight. ... [Evidence of a suggestion, teaching, or motivation to combine] must be clear and particular. ... Broad conclusory statements regarding the teaching of multiple references, standing alone, are not 'evidence.' ... [A] reference-by-reference, limitation-by-limitation analysis fails to demonstrate how the [cited] references teach or suggest their combination ... to yield the claimed invention," and a conclusion of obviousness based on such an analysis "as a matter of law, cannot

stand.” *In re Dembiczak*, 175 F.3d 994, 999, 1000, 50 USPQ2d 1614, 1617, 1618 (Fed.

Cir. 1999), emphasis added.

Dembiczak involved patent claims to “a large trash bag made of orange plastic and decorated with lines and facial features, allowing the bag, when filled with trash or leaves, to resemble a Halloween-style pumpkin, or jack-o'-lantern.” *Dembiczak*, 996, 1616. The prior art cited by the Board included: a book describing how to teach children to make a “Crepe Paper Jack-O-Lantern;” a book describing a method of making a “paper bag pumpkin” by stuffing a bag with newspapers, painting it orange, and then painting on facial features with black paint; a U.S. Patent describing a bag apparatus wherein the bag closure is accomplished by the use of folds or gussets in the bag material; design patents issued to Dembiczak; and prior art “conventional” plastic lawn or trash bags. The Federal Circuit held that the claimed pumpkin-style trash bag was not obvious because there was no clear, particular motivation to combine the cited references.

This holding of *Dembiczak* that evidence of motivation to combine must be clear and particular to establish obviousness has been emphasized over and over again by the Federal Circuit since *Dembiczak* was decided. It was strongly reemphasized in *Ruiz v. A.B. Chance Co.*, 57 USPQ2d 1161 (Fed. Cir. 2000):

In order to prevent a hindsight-based obviousness analysis, we have clearly established that the relevant inquiry for determining the scope and content of the prior art is whether there is a reason, suggestion, or motivation in the prior art or elsewhere that would have led one of ordinary skill in the art to combine the references. See, e.g., In re Rouffet, 149 F.3d 1350, 1359, 47 USPQ2d 1453, 1459 (Fed. Cir. 1998) (“[T]he Board must identify specifically . . . the reasons one of ordinary skill in the art would have been motivated to select the references and to combine them to render the claimed invention obvious.”); In re Dembiczak, 175 F.3d at 999, 50 USPQ2d at 1617

("Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references."). "Determining whether there is a suggestion or motivation to modify a prior art reference is one aspect of determining the scope and content of the prior art, a fact question subsidiary to the ultimate conclusion of obviousness." Sibia Neurosciences, Inc. v. Cadus Pharma. Corp., 225 F.3d 1349, 1356, 55 USPQ2d 1927, 1931 (Fed. Cir. 2000); Tec Air, Inc. v. Denso Mfg., Inc., 192 F.3d 1353, 1359, 52 USPQ2d 1294, 1298 (Fed. Cir. 1999) (stating that the factual underpinnings of obviousness include whether a reference provides a motivation to combine its teachings with those of another reference).

... there is "a general rule that combination claims can consist of combinations of old elements as well as new elements," Clearstream Wastewater Sys. v. Hydro-Action, Inc., 206 F.3d 1440, 1446, 54 USPQ2d 1185, 1189-90 (Fed. Cir. 2000), "[t]he notion . . . that combination claims can be declared invalid merely upon finding similar elements in separate prior patents would necessarily destroy virtually all patents and cannot be the law under the statute, § 103." Panduit Corp. v. Dennison Mfg. Co., 810 F.2d 1561, 1575, 1 USPQ2d 1593, 1603 (Fed. Cir. 1987); Arkie Lures, Inc. v. Gene Larew Tackle, Inc., 119 F.3d 953, 957, 43 USPQ2d 1294, 1297 (Fed. Cir. 1997) ("It is insufficient to establish obviousness that the separate elements of the invention existed in the prior art, absent some teaching or suggestion, in the prior art, to combine the elements.").

Ruiz at 1167

The motivation cited in the Office Action for the proposed combination is as follows:

"One would have been motivated to do so because both nipple aspiration and ductal lavage are non-invasive and can effectively obtain ductal epithelial cells as shown by Sauter and

JAMA reference. Moreover, one of ordinary skill in the art would have a reasonable expectation of success to obtain ductal epithelial cells by nipple aspiration or ductal lavage of breast milk duct because Sauer *et al.* teach nipple aspiration and JAMA references a method of obtaining ductal cells by lavage or breast milk ducts. Moreover, it would have been *prima facie* obvious and one would have been motivated to use the estrogen receptor status obtained by Fabian to further provide information regarding the hormonal treatment (such as estrogen antagonist) response in view of the teachings of Knight. One of ordinary skill in the art would have a reasonable expectation of success to do so because Knight has shown that estrogen receptor can predict patient response to hormonal treatment.” Office Action at page 7-8.

This statement does not provide the clear, particular suggestion in the art for making the specific claimed combination as is required under *In re Dembiczak*. The claims here are no more obvious than those at issue in *Dembiczak*. No clear, particular suggestion or motivation in the prior art to make the specific method for “ identifying asymptomatic patients who have a likelihood of benefiting from the administration of an estrogen activity modulator for risk reduction or therapeutic treatment of breast cancer, said method comprising: providing a ductal fluid sample from at least one duct of a breast of the patient wherein said sample is obtained by nipple aspiration of the milk ducts or by ductal lavage of at least one breast milk duct; and examining the ductal fluid sample to determine the presence of an estrogen receptor on precancerous or cancerous ductal epithelial cells, wherein asymptomatic patients determined to have the presence of an estrogen receptor on precancerous or cancerous ductal epithelial cells are considered likely to benefit from administration of an estrogen activity modulator for risk reduction or therapeutic treatment of breast cancer.

Prima facie obviousness has not been established under such conditions. Neither Fabian, *et al.*, Sauter *et al.*, JAMA, or Knight *et al.*, either alone or in combination, teach or suggest all the limitations of the present claims. None of the cited references teach a method of ductal lavage.

The obviousness rejection is based on hindsight from these disparate references to provide random elements of the claims. There is no clear, particular motivation in the references to reach the claimed invention. Withdrawal of this rejection under 35 USC 103(a) is respectfully requested.

The Double Patenting Rejections

The Examiner has previously rejected claims 1, 7 and 15 on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 1, 2, 11, 13, and 22 of USP 6,642,009. The Applicants would note that current Application 10/608,225 claims priority from Provisional Application 60/117,281 filed January 26, 1999 while USP 6,642,009 claims priority from Provisional Application 60/166,100 filed November 17, 1999. Thus, commonly-owned USP 6,642,009 does not qualify as prior art under 35 U.S.C. 102(e), (f), or (g). For this reason, the Applicants respectfully submit that the non-statutory obviousness-type double patenting rejection should be withdrawn.

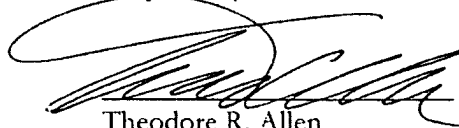
REMARKS

In light of the arguments presented above, Applicants respectfully submit that the claims are in condition for allowance. Early notice to this effect is solicited. A two month extension of time is hereby requested.

It is not believed that any additional extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 502855 referencing attorney docket number 12.003011 DIV.

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